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(54) Title: IMPROVED METHOD FOR ERADICATION OF *HELICOBACTER PYLORI*

(57) Abstract

The invention provides methods for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *Helicobacter pylori* in a patient requiring said treatment and/or prevention, which comprise administering to the patient a therapeutically effective amount of a first antibiotic which is an ansamycin and a therapeutically effective amount of at least a second antibiotic or antimicrobial agent. The invention also provides pharmaceutical compositions for use in the methods of the invention.

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Improved Method for Eradication of *Helicobacter Pylori*

Technical Field

This invention relates to pharmaceutical compositions and therapeutic methods for the treatment and/or prevention of recurrence of gastrointestinal disorders associated with infection by Helicobacter pylori (*H. pylori*).

Background

Helicobacter pylori has been found to cause chronic histological gastritis and peptic ulcer disease, such as gastric and duodenal ulcer. It also appears to cause a condition called non-ulcer dyspepsia where Helicobacter pylori causes inflammation in the stomach which is histologically associated with indigestion and epigastric pain. Helicobacter pylori is also thought to have a role in the causation of stomach cancer and its eradication may be instrumental in causing cure of ulcer disease, a reversal of a proportion of patients with non-ulcer dyspepsia, and prevention of gastric cancer development in those who may be predisposed to it.

Until recent times, *H. pylori* has been found to be difficult to eradicate using known chemotherapeutic agents. Although many antibiotics can suppress *H. pylori* growth *in vivo* the mucosal concentration appears to be inadequate and penetration of the usual gastric mucus layer is poor. Furthermore, there is frequently more than one infecting agent within the mucosa and hence, sensitivities of the various bacteria may vary within one patient and within one region of the mucosa. The development of adequate *in vivo* eradication methods for chronic *H. pylori* infection has therefore been difficult. Furthermore, single antibiotics are almost never adequate for use and double antibiotic combinations have also resulted in poor eradication rates. A further major looming problem progressively affecting current eradication therapies is the rapid development of clarithromycin resistance worldwide. The proportion of *H. pylori* infections which are resistant to clarithromycin is increasing by from 2-5% per year. Resistance is developing faster in the countries where clarithromycin is being used frequently; in particular, USA and Europe. Hence, new methods for eradication of *H. pylori* are urgently required. In addition, salvage therapies for patients who have failed first time therapy are also unavailable and such treatments are becoming in demand as more and more patients undergo therapy and fail initial eradication attempts.

It is therefore an object of the present invention to provide a novel pharmaceutical composition for the treatment and/or prevention of recurrence of gastrointestinal disorders associated with *H. pylori*.

It is a further object of the invention to provide methods for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

Disclosure of the Invention

The present inventor has found that the use of a novel combination antibiotic therapy not only results in high initial eradication rates of *H. pylori* but also can be used as a salvage therapy. There is a large volume of literature describing numerous and varying combinations of antimicrobial agents for *H. pylori* eradication, to a large extent due to the fact that it is difficult to predict clinically which combination might work and which will be unsuccessful. Indeed, persons skilled in the art cannot - from *in vitro* studies or from their previous experience - simply predict the success or failure of a particular regime.

Rifampicin is an antimycobacterial antibiotic used in the treatment of tuberculosis. Recently, its semi-synthetic derivative, an ansamycin called rifabutin which is currently indicated for the treatment of tuberculosis or *Mycobacterium avium* complex infection, has been described as having *in vitro* activity against Helicobacter pylori when tested in culture. In the present invention combinations containing an ansamycin have been found to be clinically effective in eradicating *H. pylori*.

In a first embodiment, the present invention provides a pharmaceutical composition for the treatment of gastrointestinal disorders associated with *H. pylori* infection including a first antibiotic which is an ansamycin, and at least a second antibiotic or antimicrobial agent, together with at least one pharmaceutically acceptable carrier, diluent, adjuvant or excipient.

In a second embodiment, the invention provides a method for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient requiring said treatment and/or prevention, which method comprises administering to said patient sequentially or simultaneously a therapeutically effective amount of a first antibiotic which is an ansamycin and a therapeutically effective amount of at least a second antibiotic or antimicrobial agent.

Typically, a method of treatment in accordance with the invention results in the eradication of *H. pylori* from the patient who is treated.

In a third embodiment, the invention further provides the use of a therapeutically effective amount of a first antibiotic which is an ansamycin and a therapeutically effective amount of at least a second antibiotic or antimicrobial agent for the manufacture of a medicament for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

In a fourth embodiment, the invention still further provides a therapeutically effective amount of a first antibiotic which is an ansamycin and a therapeutically effective amount of at least a second antibiotic or antimicrobial agent when used for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

Typically in the embodiments of the invention the ansamycin is selected from the group consisting of rifamycin, rifaximin, rifampicin, rifabutin and pharmaceutically acceptable salts thereof. More typically, the ansamycin is rifampicin or rifabutin. Preferably, the ansamycin is rifabutin.

The pharmaceutical composition of the invention includes, in addition to the an ansamycin, one or more other antibiotics or antimicrobial agents. Typically, where the patient to whom the pharmaceutical composition is to be administered has previously not been treated for *H. pylori* infection, the pharmaceutical composition of the invention includes an ansamycin, typically rifabutin, and just one other antibiotic or antimicrobial agent. In other cases, the pharmaceutical composition typically includes an ansamycin, typically rifabutin, and two different antibiotics or antimicrobial agents. In severe cases, or in cases where a resistant strain of *H. pylori* is encountered, three, four or even more antibiotics may be included together with the ansamycin.

Similarly, in the method of the second embodiment and in the third and fourth embodiments of the invention an ansamycin and a single other antibiotic or antimicrobial agent may be used, but more typically an ansamycin and two different other antibiotics or antimicrobial agents, or three, four or more, may be used.

In the method of the second embodiment, the active agents, namely the ansamycin and the one or more other antibiotics or antimicrobial agents, may be administered simultaneously or sequentially, in any order.

The pharmaceutical composition of the first embodiment may further include a proton pump inhibitor (PPI). Similarly, a method of the second embodiment may further include the administration of a proton pump inhibitor. The inclusion of a PPI can help to enhance the eradication rate of *H. pylori* and can improve the patient's symptoms, since patients are often dyspeptic at the beginning of the treatment. The administration of the PPI in the method of the second embodiment may be separate from the administration of the ansamycin and other antibiotic(s) or antimicrobial agent(s), or the PPI may be co-administered with the ansamycin and/or one or more other antibiotics or antimicrobial agents. Suitable PPIs include omeprazole, pantoprazole, lansoprazole and rabeprazole.

Similarly, the invention also provides the use of a therapeutically effective amount of an ansamycin, a therapeutically effective amount of at least one other antibiotic or antimicrobial agent, and a therapeutically effective amount of a proton pump inhibitor for the manufacture of a medicament for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

The invention further provides a therapeutically effective amount of an ansamycin, a therapeutically effective amount of at least one other antibiotic or antimicrobial agent and a therapeutically effective amount of a proton pump inhibitor

when used for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

The antibiotic(s) or antimicrobial agent(s) included in the pharmaceutical composition, method or use of the invention may be selected from the penicillins, bismuth compounds, tetracyclines, nitroimidazoles, quinolones, lincosamides, macrolides and cephalosporins. Examples of the penicillins include penicillin G, penicillin V, pheneticillin, propicillin, methicillin, oxacillin, cloxacillin, dicloxacillin, flucloxacillin, nafcillin, ampicillin, amoxycillin, bacampicillin, hetacillin, metampicillin, pivampicillin, talampicillin, carbenicillin, carfecillin, carindacillin, sulbenicillin, ticarcillin, azlocillin, mezlocillin, piperacillin, apalcillin, temocillin, mecillinam and pivmecillinam. Examples of bismuth compounds include bismuth subcitrate, bismuth aluminate, bismuth oxide, bismuth salicylate, bismuth sugballate, bismuth tannate, bismuth phosphate, bismuth tribromphenate, bismuth subcarbonate, bismuth subnitrate, and mixtures thereof. Examples of the tetracyclines including tetracycline hydrochloride, oxytetracycline, doxycycline, methacycline, chlortetracycline, demeclocycline and minocycline. Examples of nitroimidazoles include metronidazole, tinidazole, nimorazole, ornidazole and orthanidazole. Examples of quinolones include ciprofloxacin, norfloxacin, enoxacin, lomefloxacin, pefloxacin, amifloxacin, fleroxacin, levofloxacin, nadifloxacin, rufloxacin, sparfloxacin, tosufloxacin and ofloxacin. Examples of lincosamides include lincomycin and clindamycin. Examples of macrolides include erythromycin, spiramycin, oleandomycin, triacetyloleandomycin, clarithromycin, roxithromycin, josamycin, kitsamycin, midecamycin, miocamycin, rokitamycin, dirithromycin,, rosarimycin, flurithromycin and azithromycin. Examples of cephalosporins include cephalexin, pivcephalexin, cephalothin, cephazolin, cefroxadine, cefadroxil, cefatrizine, cefaclor, cefprozil, cephradine, and second as well as third generation cephalosporins such as cephamandole, cefuroxime, cefuroxime axetil, cefonicid, ceforanide, cefotiam, cefotaxime, cefmenoxime, cefodizime, ceftizoxime, cefiximine, cefdinir, cefetamet pivoxil, cefpodoxime proxetil, ceftibuten, ceftazidime, ceftoperazone, cefpiramide, cefsoludin, cefepime, cefpirome and ceftriaxone, and related compounds such as oxycephalosporins including latamoxef, and cephamycins such as cefoxitin, cefmetazole, cefotetan, cefbuperazone and cefminox.

Typically, in one form of the invention rifabutin is used in combination with a penicillin as a first antibiotic, and a bismuth compound, as a second antimicrobial agent. An alternative second antimicrobial agent in this form of the invention is a tetracycline.

In one preferred embodiment of the invention, in previously untreated patients rifabutin can be used solely with clarithromycin, or rifabutin can be used in a triple therapy format with clarithromycin and a PPI such as pantoprazole. These all can be

given in twice daily dosage or up to five times daily for more resistant strains. In the treatment of highly resistant strains where salvage therapy is required, three, four or even more of the antibiotics or antimicrobial agents exemplified above can be combined with rifabutin to affect a cure of Helicobacter pylori infection.

One preferred combination for use in the pharmaceutical compositions, methods and other embodiments of the present invention in patients who do not harbour resistant *H. pylori* is a combination of rifabutin, clarithromycin and pantoprazole. Another preferred combination is a combination of rifabutin, amoxycillin and a PPI such as omeprazole, pantoprazole or lansoprazole. A further preferred combination is a combination of rifabutin, tetracycline and pantoprazole. These combinations can be given for between three and 21 days to affect a cure.

In a further combination rifabutin can be combined with bismuth subcitrate, amoxycillin, and a PPI such as pantoprazole or omeprazole. This combination has the added advantage that the dosage of each agent can be reduced, compared to clinically standard doses (with a reduction in the possibility of side effects as well as a reduction in cost) and the duration of treatment shortened, for example to 7 days.

Pharmaceutical compositions of the invention include one or more pharmaceutically acceptable excipients, adjuvants, diluents or carriers which are generally known in the art.

Pharmaceutical compositions of the invention or for administration in a method of the invention may be prepared by means known in the art for the preparation of pharmaceutical compositions including blending, grinding, homogenising, suspending, dissolving, emulsifying, dispersing and where appropriate, mixing of the active agents together with one or more excipients, diluents, carriers and adjuvants.

For oral administration, the pharmaceutical composition may be in the form of tablets, lozenges, pills, troches, capsules, elixirs, powders, including lyophilised powders, solutions, granules, suspensions, emulsions, syrups and tinctures. Slow-release, or delayed-release, forms may also be prepared, for example in the form of coated particles, multi-layer tablets or microgranules.

Solid forms for oral administration may contain pharmaceutically acceptable binders, sweeteners, disintegrating agents, diluents, flavourings, coating agents, preservatives, lubricants and/or time delay agents. Suitable binders include gum acacia, gelatin, corn starch, gum tragacanth, sodium alginate, carboxymethylcellulose or polyethylene glycol. Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharine. Suitable disintegrating agents include corn starch, methylcellulose, polyvinylpyrrolidone, xanthan gum, bentonite, alginic acid or agar. Suitable diluents include lactose, sorbitol, mannitol, dextrose, kaolin, cellulose, calcium carbonate, calcium silicate or dicalcium phosphate. Suitable flavouring agents include peppermint oil, oil of wintergreen, cherry, orange or raspberry flavouring. Suitable

coating agents include polymers or copolymers of acrylic acid and/or methacrylic acid and/or their esters, waxes, fatty alcohols, zein, shellac or gluten. Suitable preservatives include sodium benzoate, vitamin E, alpha-tocopherol, ascorbic acid, methyl paraben, propyl paraben or sodium bisulphite. Suitable lubricants include magnesium stearate, stearic acid, sodium oleate, sodium chloride or talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate.

Liquid forms for oral administration may contain, in addition to the active agents, a liquid carrier. Suitable liquid carriers include water, oils such as olive oil, peanut oil, sesame oil, sunflower oil, safflower oil, arachis oil, coconut oil, liquid paraffin, ethylene glycol, propylene glycol, polyethylene glycol, ethanol, propanol, isopropanol, glycerol, fatty alcohols, triglycerides or mixtures thereof.

Suspensions for oral administration may further include dispersing agents and/or suspending agents. Suitable suspending agents include sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, poly-vinyl-pyrrolidone, sodium alginate or cetyl alcohol. Suitable dispersing agents include lecithin, polyoxyethylene esters of fatty acids such as stearic acid, polyoxyethylene sorbitol mono- or di-oleate, -stearate or -laurate, polyoxyethylene sorbitan mono- or di-oleate, -stearate or -laurate and the like.

Emulsions for oral administration may further include one or more emulsifying agents. Suitable emulsifying agents include dispersing agents as exemplified above or natural gums such as gum acacia or gum tragacanth.

Dosages of the ansamycin and the other antibiotic(s) or antimicrobial agent(s) in the methods of the invention are in accordance with their generally known and safe dosage ranges. For example, dosages for the antimicrobial agents are well known to medical practitioners, as are suitable dosages for rifabutin when it is administered for the treatment of tuberculosis or *Mycobacterium avium* complex infection. Thus, for example the typical daily dosage of rifabutin in a method of the invention is in the range of about 50mg to about 2000mg, more typically about 450mg . For tetracycline the typical daily dosage is in the range of from about 50mg to about 4000mg, more typically about 1500mg; for amoxycillin, the typical daily dosage is in the range of from about 100mg to about 5000mg, more typically about 150omg; for bismuth the typical daily dosage is in the range of from about 50mg to about 2000mg, more typically about 300mg; and for pantoprazole the typical daily dosage is in the range of from about 20mg to about 500mg, more typically about 120mg.

The agents may be administered once per day or more frequently, in divided doses. For example, rifabutin can be administered from twice daily up to five times daily. Treatment is typically continued until eradication of the *H. pylori* infection has been completed. Usually, the treatment is continued for from three days to 14 days, but can continue for up to 28 days. Dosages may be varied during the course of

treatment, depending on the attending physician's assessment of the progress of the patient, or they may be maintained substantially the same throughout the treatment.

In addition, for resistant strains the patient can be pretreated with known immunising agents for Helicobacter pylori and then treated with any selected combination of the rifabutin-containing combination therapies of the present invention.

EXAMPLES

Example 1

The Table presents the results of testing carried out on a number of patients using the epsilon test ("E-test", AB Biodisc) which show that in all cases where there was infection by *H. pylori* which was resistant to one or both of metronidazole and clarithromycin, the infection was sensitive to rifabutin administration. The E-test is used as a graded antibiotic sensitivity detecting strip for examining resistance of *H.pylori*.

Example 2

A male patient, 37 years old, who had been unsuccessfully treated previously for *H. pylori* infection using a combination of clarithromycin, amoxycillin and omeprazole was treated by administration of 4 times daily doses of rifabutin, pantoprazole and tetracycline in amounts of 600mg, 160mg and 2000mg per day respectively. After a period of 8 days on this treatment, the *H. pylori* infection in the patient had been eradicated.

TABLE

E. Test for Metronidazole, Clarithromycin and Rifabutin

Patient ID.	Initials	Age	Sex	Urease test for *H. pylori*	Culture for H. pylori*	E. Test					
						Metronidazole		Clarithromycin		Rifabutin	
						ug/mL	Result	ug/mL	Result	ug/mL	Result
1	FA	27	m	Positive	3	>32	Resistant	<0.016	Sensitive	N/A	N/A
2	MJ	59	m	Positive	3	>32	Resistant	<0.016	Sensitive	N/A	N/A
3	KJ	61	f	Positive	3	>32	Resistant	<0.016	Sensitive	N/A	N/A
4	YW	59	m	Positive	3	>32	Resistant	<0.016	Sensitive	N/A	N/A
5	TD	60	f	Positive	2	>32	Resistant	<0.016	Sensitive	N/A	N/A
6	BL	34	f	Positive	2	>32	Resistant	<0.016	Sensitive	N/A	N/A
7	AB	67	m	Positive	1	>32	Resistant	<0.016	Sensitive	N/A	N/A
8	RR	59	f	Positive	1	N/A	N/A	<0.016	Sensitive	<0.002	Sensitive
9	CH	81	m	Positive	2	N/A	N/A	N/A	N/A	<0.002	Sensitive
10	AA	71	m	Positive	3	N/A	N/A	<0.016	Sensitive	<0.002	Sensitive
11	W	58	m	Positive	2	N/A	N/A	<0.016	Sensitive	<0.002	Sensitive
12	PM	40	f	Positive	2	N/A	N/A	<0.016	Sensitive	<0.002	Sensitive
13	OL	52	f	Positive	2	N/A	N/A	<0.016	Sensitive	<0.002	Sensitive
14	HS	29	f	Positive	2	N/A	N/A	<0.016	Sensitive	<0.002	Sensitive
15	FJ	42	m	Positive	2	N/A	N/A	<0.016	Sensitive	<0.002	Sensitive
16	MG	56	m	Positive	1	N/A	N/A	<0.016	Sensitive	<0.002	Sensitive
17	HC	52	f	Positive	3	N/A	N/A	<0.016	Sensitive	<0.002	Sensitive
18	CL	43	m	Positive	2	N/A	N/A	<0.016	Sensitive	<0.002	Sensitive
19	SR	52	m	Positive	2	N/A	N/A	<0.016	Sensitive	<0.002	Sensitive
20	WJ	66	m	Positive	1	N/A	N/A	<0.016	Sensitive	<0.002	Sensitive
21	DN	58	f	Positive	3	N/A	N/A	<0.016	Sensitive	<0.002	Sensitive
22	DF	26	m	Positive	3	N/A	N/A	<0.016	Sensitive	<0.002	Sensitive
23	HM	39	m	Positive	3	>32	Resistant	>4	Resistant	<0.002	Sensitive
24	LL	22	f	Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
25	DJ	48	f	Positive	2	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
26	BM	52	f	Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive

27	EHK	32	f	Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
28	FM	63	f	Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
29	MM	27	m	Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
30	HF	55	m	Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
31	BA	41	m	Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
32	LIS			Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
33	IN			Positive	2	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
34	PJ			Positive	2	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
35	TH			Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
36	FE			Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
37	BN	72	f	Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
38	AM	62	m	Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
39	TR	56	m	Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
40	GJ	64	f	Positive	2	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
41	HE	91	f	Positive	1	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
42	HA	51	m	Positive	3	<0.125	Sensitive	<0.016	Sensitive	<0.002	Sensitive
43	LE	40	m	Positive	1	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
44	CE	77	f	Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
45	MG	74	f	Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
46	GP	79	f	Positive	3	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
47	BD	73	f	Positive	2	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive
48	MC	31	f	Positive	2	<2	Sensitive	<0.016	Sensitive	<0.002	Sensitive
49	LJ	58	m	Positive	3	>4	Resistant	<0.016	Sensitive	<0.002	Sensitive
50	IE	49	f	Positive	2	N/A	N/A	N/A	N/A	N/A	N/A
51	AM	64	m	Positive	3	N/A	N/A	N/A	N/A	N/A	N/A
52	PG	64	f	Positive	1	>32	Resistant	<0.016	Sensitive	<0.002	Sensitive

* 1: light

2: medium

3: heavy

N/A: results not available

Claims

1. A pharmaceutical composition for the treatment of gastrointestinal disorders associated with *H. pylori* infection including a first antibiotic which is an ansamycin, and at least a second antibiotic or antimicrobial agent, together with at least one pharmaceutically acceptable carrier, diluent, adjuvant or excipient.

2. A pharmaceutical composition according to claim 1, further including a proton pump inhibitor.

3. A pharmaceutical composition according to claim 1 or claim 2, including, in addition to said ansamycin, at least two antibiotics or antimicrobial agents.

4. A pharmaceutical composition according to claim 1 wherein the second antibiotic or antimicrobial agent is selected from the group consisting of penicillins, bismuth compounds, tetracyclines, nitroimidazoles, quinolones, lincosamides, macrolides and cephalosporins.

5. A pharmaceutical composition according to claim 2, wherein the proton pump inhibitor is selected from omeprazole, pantoprazole, rabeprazole and lansoprazole.

6. A pharmaceutical composition according to claim 5, wherein the proton pump inhibitor is pantoprazole.

7. A pharmaceutical composition according to claim 6, wherein said ansamycin is rifabutin, and said second antibiotic or antimicrobial agent is tetracycline.

8. A pharmaceutical composition according to claim 1, wherein said ansamycin is rifabutin.

9. A pharmaceutical composition according to claim 7, wherein said second antimicrobial agent is selected from clarithromycin, amoxycillin and tetracycline.

10. A pharmaceutical composition according to claim 1 including rifabutin, a penicillin and a bismuth compound.

11. A method for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient requiring said treatment and/or prevention, which method comprises administering to said patient sequentially or simultaneously a therapeutically effective amount of a first antibiotic which is an ansamycin and a therapeutically effective amount of at least a second antibiotic or antimicrobial agent.

12. A method according to claim 11, further including administering to said patient a proton pump inhibitor.

13. A method according to claim 11 or claim 12, wherein, in addition to said ansamycin, at least two antibiotics or antimicrobial agents are administered.

14. A method according to claim 11 wherein said second antibiotic or antimicrobial agent is selected from the group consisting of penicillins, bismuth

compounds, tetracyclines, nitroimidazoles, quinolones, lincosamides, macrolides and cephalosporins.

15. A method according to claim 12, wherein said proton pump inhibitor is selected from omeprazole, pantoprazole, rabeprazole and lansoprazole.

16. A method according to claim 15, wherein said proton pump inhibitor is pantoprazole.

17. A method according to claim 16, wherein said ansamycin is rifabutin, and said second antibiotic or antimicrobial agent is tetracycline.

18. A method according to claim 11, wherein said ansamycin is rifabutin.

19. A method according to claim 12, wherein the antimicrobial agent is selected from clarithromycin, amoxycillin and tetracycline.

20. A method according to claim 11 wherein rifabutin, a penicillin and a bismuth compound are administered to said patient.

21. Use of a therapeutically effective amount of a first antibiotic which is an ansamycin and a therapeutically effective amount of at least a second antibiotic or antimicrobial agent for the manufacture of a medicament for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

22. Use according to claim 21 of a therapeutically effective amount of a first antibiotic which is an ansamycin, a therapeutically effective amount of at least a second antibiotic or antimicrobial agent and a therapeutically effective amount of a proton pump inhibitor for the manufacture of a medicament for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

23. Use of therapeutically effective amounts of at least three antibiotics or antimicrobial agents for the manufacture of a medicament for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient, wherein one of said antibiotics or antimicrobial agents is an ansamycin.

24. Use according to claim 21 wherein said second antibiotic or antimicrobial agent is selected from the group consisting of penicillins, bismuth compounds, tetracyclines, nitroimidazoles, quinolones, lincosamides, macrolides and cephalosporins.

25. Use according to claim 22, wherein said proton pump inhibitor is selected from omeprazole, pantoprazole, rabeprazole and lansoprazole.

26. Use according to claim 25, wherein said proton pump inhibitor is pantoprazole.

27. Use according to claim 26, wherein said ansamycin is rifabutin, and said second antibiotic or antimicrobial agent is tetracycline.

28. Use according to claim 21, wherein said ansamycin is rifabutin.

29. Use according to claim 22, wherein said second antimicrobial agent is selected from clarithromycin, amoxycillin and tetracycline.

30. Use according to claim 21 of rifabutin, a penicillin and a bismuth compound for the manufacture of a medicament for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

31. A therapeutically effective amount of a first antibiotic which is an ansamycin and a therapeutically effective amount of at least a second antibiotic or antimicrobial agent when used for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

32. A therapeutically effective amount of a first antibiotic which is an ansamycin and a therapeutically effective amount of at least a second antibiotic or antimicrobial agent and a therapeutically effective amount of a proton pump inhibitor when used for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

33. Therapeutically effective amounts of at least three antibiotics or antimicrobial agents when used for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient, wherein one of said antibiotics or antimicrobial agents is an ansamycin.

34. A therapeutically effective amount of a first antibiotic which is an ansamycin and a therapeutically effective amount of at least a second antibiotic or antimicrobial agent selected from the group consisting of penicillins, bismuth compounds, tetracyclines, nitroimidazoles, quinolones, lincosamides, macrolides and cephalosporins, when used for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

35. A therapeutically effective amount of a first antibiotic which is an ansamycin and a therapeutically effective amount of at least a second antibiotic or antimicrobial agent and a therapeutically effective amount of a proton pump inhibitor selected from omeprazole, pantoprazole, rabeprazole and lansoprazole, when used for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

36. A therapeutically effective amount of a first antibiotic which is an ansamycin and a therapeutically effective amount of at least a second antibiotic or antimicrobial agent and a therapeutically effective amount of pantoprazole when used for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

37. A therapeutically effective amount of rifabutin and a therapeutically effective amount of tetracycline and a therapeutically effective amount of pantoprazole when used for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

38. A therapeutically effective amount of a first antibiotic which is rifabutin and a therapeutically effective amount of at least a second antibiotic or antimicrobial agent when used for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

39. A therapeutically effective amount of a first antibiotic which is an ansamycin and a therapeutically effective amount of at least a second antibiotic or antimicrobial agent selected from clarithromycin, amoxycillin and tetracycline, and a therapeutically effective amount of a proton pump inhibitor when used for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

40. A therapeutically effective amount of rifabutin, a therapeutically effective amount of penicillin and a therapeutically effective amount of a bismuth compound when used for the treatment and/or prevention of recurrence of a gastrointestinal disorder associated with *H. pylori* in a patient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00321

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 31/445, 31/71, 31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC AS ABOVE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT CAPLUS MEDLINE: (rifabutin, rifamycin, rifaximin, rifampicin OR ansamycin) AND (helicobacter, pylori OR camylobacter pylori)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Medline Abstract Accession No. 98219485, De Giorgio R *et al.* Rifaximin and *Helicobacter pylori* eradication, *Eur. Rev. Med. Pharmacol. Sci.*, Jul-Aug 1997, 1(4):105-110	1-40
X	Vaira D *et al.*, Rifaximin suspension for the eradication of *Helicobacter pylori*, *Curr. Ther. Res.*, May 1997, 58(5):300-308	1-40
X	Holton J *et al.*, The susceptibility of. *Helicobacter pylori* to the rifamycin, rifaximin, J. *Antimicrob. Chemother.* April 1995, 35(4):545-549	1-40

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 May 1999	25 MAY 1999
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer T. SUMMERS Telephone No.: (02) 6283 2291

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 99/00321

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, Y	Kunin CM, Antimicrobial activity of rifabutin, *Clin. Infect. Dis.*, April 1996, 22(Suppl 1):S3-S14 Entire document ,including page S9 column 1 lines 31-37 and page S10 column 1 lines 23-26	1-40
Y	WO 97/02039 A (PHARMACIA & UPJOHN SPA) 23 January 1997	1-40
X	Gevaudan MJ *et al.*, Intra-macrophagic activity of antibiotics combinations against *Mycobacterium marinum, Pathol Biol. (Paris),* May 1991, 39(5):436-441 Abstract, Table III	1-10
X	Shafran SD *et al.*, A comparison of two regimens for the treatment of *Mycobacterium avium* complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, etambutol, clofazaimine, aand ciprofloxacin. Canadian HIV Trials Network Protocol 010 Study Group, *N. Engl. J. Med.*, 8 August 1996, 335(6):377-383	1-10
X	Yaiko DM *et al.*, In vitro activities of rifabutin, azithromycin, cipofloxacin, clarithromycin, clofazimine, ethambutol, and amikacin in combinations of two, three and four drugs against *Mycobacterium avium, Antimicrob. Agents. Chemother*, March 1996, 40(3):743-749	1-10
P, X	WO 98/43667 A (BORODY, Thomas Julius) 8 October 1998	1-10

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU 99/00321

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member
WO9702039	EP836477
WO9843667	AU67127/98

END OF ANNEX